## Special Article

# Advances in Alternative Pharmacotherapy of ADHD

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*Several alternatives to psychostimulants have been developed and expanded the variability of the treatment of ADHD. Clonidine is a good option for managing core behavioral symptoms, especially hyperactivity and impulsivity. Bupropion and venlafaxine seem potentially promising. Significant new options include norepinephrine reuptake inhibitors, such as atomoxetine, and possibly selective dopamine agonists. Central anticholinesterases, such as donepezil, may improve core ADHD symptoms.*

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Attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder with major presenting symptoms of inattention, hyperactivity, and impulsivity. Children with ADHD represent a heterogenous population and display great variation in the degree of their symptoms and in the situational pervasiveness of their ADHD[1]. Its etiology remains unknown although several genetic studies suggest the likelihood of genetic origin[2-3].

Since the first systemic evaluation of benefit of stimulant medication on children in 1937 by Bradley [4], psychopharmacotherapy of ADHD has evolved enormously, especially in the past two decades. Various kinds of medications have been introduced in the treatment of ADHD both in the category of stimulants (methylphenidate, dextroamphetamine, pemoline, and amphetamine compounds) and non-stimulants (tricyclic antidepressants, non-tricyclic antidepressants, alpha-2 noradrenergic agonists, etc.)

Stimulants are the first line of medication in the treatment of ADHD. The efficacy of stimulants has been evaluated convincingly and several meta-analyses have been conducted. Spencer et al[5] reviewed the available literature on stimulants and found 155 controlled studies, mostly in school-age children, in support for efficacy and safety, with an average response of 70%. Tricyclic antidepressants (TCAs) are another class of drugs most studied in ADHD. From the same review, there had been 29 studies evaluating the efficacy and safety of TCAs, with 27 (93%) out of the 29 studies reported either moderate or robust response rate to TCAs in ADHD.

In spite of the established efficacy of stimulants and TCAs, alternative treatments of ADHD are still in need. In clinical practice, cases who do not respond to stimulants and TCAs are not uncommon. Some patients cannot tolerate side effects, for instance, loss of appetite and weight loss in stimulants, or sedation and anticholinergic side effect in TCAs. With different drug regulation laws, stimulants may not be available in some countries. Furthermore, in ADHD cases with comorbidity, the need for medication to tailor individual symptoms are even mor complicated, for example, a case of ADHD with Tourette syndrome, ADHD with comorbid depression, etc.

In the present review, the author tried to cover all the advances in research on alternative pharmacotherapy of ADHD.

### Clonidine

Clonidine is a presynaptic $\alpha_2$-adrenergic autoreceptor agonist with its effect in reduction of noradrenergic transmission. It has several indications in medicine and psychiatry such as hypertension, drug withdrawal, tic disorder, and PTSD.

Despite its wide use in ADHD children, systematic trials on clonidine have been scarce. Conner et al.[6] used meta-analysis to review the literature on the clinical use of clonidine to treat symptoms of ADHD. Out of 39 reports, only 11 studies could be included in the analysis. The findings indicated that clonidine demonstrated positive treatment effects in all 11 studies analysed and across all different observers (clinician,

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parent, teacher) of behaviors. The overall effect size of clonidine for symptoms of ADHD was 0.58 +/- 0.16 , which was considered to be moderate in size. Taking comorbidity into account, the effect size of clonidine in ADHD-alone group appeared greater than in ADHD with comorbid tic disorder. The prevalence of treatment-emergent side effects was high, with sedation and irritability reported in more than half of the analysed studies.

One of the ongoing, controversial debates in child psychiatry is about the safety of combining clonidine with methylphenidate in the treatment of ADHD. Swanson et al[7] raised a concern after a report of 4 sudden unexplained deaths occurred in children while receiving clonidine in combination with methylphenidate. This led some clinicians to withdraw clonidine from their regimen. Wilens and Spencer[8] argued against that, given the complicated underlying medical conditions in all four reported cases, causal mechanisms could not be drawn to attribute any deaths to clonidine, methylphenidate, or their combination. However, Swanson et al[9], using statistical calculation, still considered the use of the combination of methylphenidate and clonidine to be ill-advised. The time to be most cautious, according to Swanson, is when clonidine effects are at peak and methylphenidate effects are waning, or when methylphenidate effects are at peak and clonidine effects are waning or rebound effects are emerging.

**Bupropion**

Bupropion is an antidepressant in the aminoketone class with agonistic effects mainly on noradrenergic and to a lesser extent dopaminergic system. Its serotonergic properties are even less pronounced. It is an established treatment for adult depression and eating disorder. It is also commonly used to assist smoking cessation.

Bupropion has been introduced to the treatment of adult ADHD with successful outcome. Wilens et al[10] reported a double-blind, placebo-controlled, randomised, parallel 6-week trial comparing patients receiving sustained-release bupropion to patients receiving placebo. Of the 40 subjects enrolled and 38 completed the study, bupropion treatment was associated with a significant change in ADHD symptoms more than placebo.

Studies of bupropion in children and adolescents are also auspicious. In a four-centre, double-blind, placebo-controlled trial in 109 children aged 6-12 years, Conners et al.[11] demonstrated that bupropion reduced hyperactivity and aggression in a group of children with conduct and attention problems. The effects, however, were somewhat less robust than the meta-analyses of standard stimulant drug effects. In contrast, Barrrickman et al[12] directly compared bupropion and methylphenidate in double-blind, crossover study in 15 ADHD subjects (7-17 years old) and found both were effective and did not differ in overall efficacy as treatment for ADHD. In an open-label study in 24 adolescents with comorbid ADHD and depression, Daviss et al.[13] reported that bupropion sustained-release (SR) was effective for both conditions.

Some side effects may discourage the use of bupropion in children. Severe skin rash has been reported to associate with its use in child psychiatric cases[11]. It can also aggravate tics in children with comorbid ADHD and tic disorder. The risk of drug-induced seizures relative to other antidepressants is increased by 0.4% with possible link to high doses, a previous history of seizure, and eating disorders[14]. Daviss et al[13] also suggested vigilance for medication-induced irritability and bipolarity when using bupropion SR in depressed ADHD patients.

**Venlafaxine**

Venlafaxine is a selective reuptake inhibitor of both norepinephrine and serotonin similar to TCAs. It is not like TCAs in that it has no significant affinity for histamine $H_1$, muscarinic, or $\alpha$-1 adrenergic receptors.

Three open studies suggest therapeutic effects of venlafaxine in ADHD[15-17]. While the high response rate was reported in completers, high drop out rate also occurred due to side effects such as sedation, agitation, and nausea. An open trial in 16 adolescents (mean age 11.6 years) yielded similar results with 50% response rate and 25% rate of drop out due to side effects.

Controlled trials are yet to be conducted to further address the efficacy and tolerabity of venlafaxine.

**Selective Serotonin Reuptake Inhibitors**

Open-label clinical trials in children with ADHD suggested some therapeutic benefit of fluoxetine in ADHD[18]. Nevertheless, no controlled studies have been conducted.

Possible reasons for lack of encouragement to do systematic studies regarding SSRIs in ADHD are 1) evidence of serotonergic involvement in pathophysiology of ADHD is less clear than other neurotransmitters 2) it is generally agreed from most clinical practice

that SSRIs don't seem to work well in ADHD.

**Carbamazepine**

Carbamazepine, like any antiepileptic drugs, can induce hyperactivity in children. In spite of that, by the mechanisms not clearly understood, it has been successfully used in some cases of ADHD. Silva et al [19] reviewed 10 methodologically adequate studies about carbamazepine in wide-range disorders with hyperactivity. Meta-analysis using weighted variables revealed a significant positive correlation between duration of treatment and positive outcome. In three double-blind studies, it was found that carbamazepine was a safe and effective treatment for children with features of ADHD when compared to placebo and showed an effect size equivalent to that of stimulant treatment.

Nonetheless, the inclusion of hyperactivity of any kinds in this meta-analysis means carbamazepine might work well in reducing nonspecific symptoms of hyperactivity syndrome, but might not be a preferred treatment of ADHD as diagnosed by DSM-IV or ICD-10. Several adverse effects such as sedation, rash, agranulocytosis, and hepatotoxicity also discourage the use of carbamazepine in children with ADHD.

**Atomoxetine**

Altered noradrenergic transmission could contribute to symptoms of ADHD[20]. Atomoxetine is a highly selective noradrenergic reuptake inhibitor with little affinity for other neurotransmitter systems (muscarinic, cholinergic, histaminic, serotonergic, or $\alpha_1$ and $\alpha_2$ adrenergic) and little effect on cardiac conduction, repolarization, and function[21]. It was found in 6 randomised, double-blind, placebo-controlled studies in a total of 892 children and 179 adolescents with ADHD to be clinically and statistically superior to placebo in reducing symptoms of ADHD based on parent and teacher reports with large effect size (0.6-0.8). The drug was generally well-tolerated, and treatment-emergent adverse events were mild. Possible side effects include gastrointestinal symptoms, decreased appetite, drowsiness, tachycardia, and irritability[22-25].

**Nicotine**

Nicotine directly stimulates nicotinic acetylcholine receptors, and it also promotes the release of dopamine and other neurotransmitters such as acetylcholine, serotonin and norepinephrine. Nicotine intake from cigarette smoking has been reported to improve attentiveness[26].

Levin et al[27] conducted a study to prove the usefulness of nicotine in treating the symptoms of ADHD. Six smokers with overnight smoking deprivation and 11 nonsmokers, both groups with ADHD, participated in an acute, placebo-controlled double-blind study in which the subjects were randomly given a morning dose of nicotine patch resulting in a significant overall nicotine-induced improvement on attention. This effect was significant when only the nonsmokers were considered which indicated that the improvement was not due merely to withdrawal relief. Levin et al [28] also reported that nicotine could not only improve symptoms of ADHD but also attentiveness in normal non-smoking subjects with no preexisting impairment.

Because of the health risk and abuse liability inevitably accompanying cigarette smoking, chronic administration of nicotine to alleviate ADHD is definitely not a good idea. Nonetheless, Conners [29] suggested that use of commercially available transdermal nicotine patch could lead to significant improvement in ADHD symptoms and neuropsychological functioning. Although this finding is promising considering the efficacy and the potential of transdermal patch abuse appears to be low, but the short 2-day duration of the study necessitates the reexamination of the therapeutic role of nicotinic agents in ADHD. And despite the encouraging evidences of nicotine effectiveness so far, more studies, especially from different sources of investigators, are still in need. Nicotine administration in ADHD should also be compared to conventional treatment such as stimulants. On top of that, evidences regarding effects of nicotine on the majority of ADHD cases, children and adolescents, are still lacking.

**ABT-418**

ABT-418 is a prototype of a new class of compounds referred to as selective cholinergic channel activators. ABT-418 is potent and selective agonist for $\alpha$-4 $\alpha$-2 subtype CNS nicotinic receptors. It shares some structural similarities to nicotine and equipotent to nicotine in enhancing cognitive performance in animal models. Cardiovascular side effects in humans are minimal compared to nicotine.

Wilens et al[30] reported a double-blind, placebo-controlled, randomised, crossover study comparing transdermal patch of ABT-418 to placebo in adults with ADHD. Of the 32 subjects in this 3-week trial, a significantly higher proportion of subjects were considered improved while receiving ABT-418 than while

receiving placebo. A preferential improvement was found in adults with inattentive symptom cluster of ADHD and adults with less severe symptoms. Response was not affected by psychiatric comorbidity and past or current smoking status. Adverse effects reported in this study, i.e. dizziness, nausea, headaches, and dysphoria, were similar to those described with other cholinergic agents. No cardiovascular or abnormal laboratory findings were observed during the study.

Nevertheless, response rate for ABT-418 was lower than that observed in conventional treatment trials with methylphenidate and TCAs. Moreover, the effects were more selective to attentional symptoms than hyperactive/impulsive symptoms. Further controlled trials of ABT-418 with higher dosing are needed to see whether there is a change in efficacy profile. Longer trials are also required to evaluate adverse effects, especially on the cardiovascular system, in the long run.

**Donepezil**

A cholinesterase inhibitor generally and widely used in the treatment of Alzheimer's disease is speculated to have effectiveness in ADHD. Popper [31] anecdotally reported the administration of donepezil in adults and children initially to reduce central anticholinergic effects from other medications. Unexpectedly, children with ADHD ineffectively treated by conventional agents seemed to do better in terms of sharper thinking, increased awareness of detail, and improvement in memory, well-being, organizational skills, and other executive functions. Side effects were only mild to moderate gastrointestinal symptoms in a minority of patients. The use was still only in combination with other anti-ADHD medications. Wilens et al[32] also reported case series of 5 ADHD youths aged 8-17 years treated for ADHD with donepezil with demonstrated improvement.

Much more evidences are needed before we can confidently prescribe donepezil in ADHD cases. For examples, the mechanism of action and dose-range in children and adolescents are to be understood, and well-controlled studies should be done to determine the efficacy and safety.

**Conclusions**

A substantial amount of literature supports the efficacy and safety of various alternative treatments of ADHD. However, the heterogeneity of the disorder makes the development of "ideal" drug still far away from the goal. Some medications may not work up to the satisfactory level, some may work well only in certain symptom cluster or comorbidity, some may have intolerable side effects, and potential serious, though rare, side effects of some medications are discouraging.

Studies into neurobiology and genetics underlying ADHD are in progress. In that, combined with extensive well-designed and well-controlled trials, hopefully it can lead to the development of a new generation of safe and effective treatment for ADHD.

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# ความก้าวหน้าในการรักษาโรคสมาธิสั้นด้วยยาทางเลือก

**ณัทธร พิทยรัตน์เสถียร**

*ผู้นิพนธ์ได้ทบทวนวรรณกรรมเกี่ยวกับยาที่ใช้เป็นทางเลือกในการรักษาโรคสมาธิสั้น (Attention Deficit Hyperactivity Disorder - ADHD) นอกเหนือจากยากลุ่ม psychostimulants ที่ใช้เป็นยาหลัก ยาทางเลือกทำให้การรักษามีความหลากหลายและครอบคลุมอาการต่างๆ ได้มากขึ้น รวมทั้งช่วยในกรณีที่ผลข้างเคียงจากยาหลักมีมากจนผู้ป่วยทนไม่ได้ ยาทางเลือกที่มีใช้ในปัจจุบันได้แก่ clonidine, bupropion, venlafaxine, และ atomoxetine ส่วนยาบางตัวยังอยู่ในขั้นการวิจัยถึงประโยชน์และความปลอดภัยในเด็กสมาธิสั้นเช่น nicotine และ donepezil*